AMENDMENTS TO THE SPECIFICATION

Please amend the specification to read as follows:

Page 1, lines 5 through 8:

This application is a continuation application of U.S. patent application serial No. 09/524,101, filed 3/13/2000, now U. S. patent No:--------, which is a continuation-in-part of U.S. application no. 09/268,969, filed March 16, 1999; and of U.S. application no. 60/184,373 of same title, filed February 23, 2000. The entire contents of ~~both~~ prior applications are incorporated herein by reference.

Page 4, lines 11 through 15:

Figures 1A-1~~B~~D show a CLUSTALW alignment of the amino acid sequences of the insect p53 proteins identified from *Drosophila* (Dros_p53, SEQ ID NO:2), *Leptinotarsa* (CPB_p53, SEQ ID NO:4), *Tribolium* (Trib_p53A, SEQ ID NO:6; Trib_p53B, SEQ ID NO:8), and *Heliothis* (Helio_p53, SEQ ID NO:10), with p53 sequences previously identified in human (Human_p53, SEQ ID NO:33), *Xenopus* (Xeno_p53, SEQ ID NO:34), and squid (Squid_p53, SEQ ID NO:35). Identical amino acid residues within the alignment are grouped within solid lines and similar amino acid residues are grouped within dashed lines.

Page 8, line 25 through page 9, line 5:

As used herein, "percent (%) nucleic acid sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides in the candidate derivative nucleic acid sequence identical with the nucleotides in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410; ~~http://blast.wustl.edu/blast/README.html;~~ hereinafter referred to generally as "BLAST") with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself

depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A percent (%) nucleic acid sequence identity value is determined by the number of matching identical nucleotides divided by the sequence length for which the percent identity is being reported.

Page 17, lines 20-26:

Other preferred p53 polypeptides, fragments or derivatives consist of or comprise a sequence selected from the group consisting of RICSCPKRD (SEQ ID NO:23), KICSCPKRD (SEQ ID NO:24), RVCSCPKRD (SEQ ID NO:25), KVCSCPKRD (SEQ ID NO:26), RICTCPKRD (SEQ ID NO:27), KICTCPKRD (SEQ ID NO:28), RVCTCPKRD (SEQ ID NO:29), and KVCTCPKRD (SEQ ID NO:30) (i.e. sequences of the formula: (R or K)(I or V)C(S or T)CPKRD). Additional preferred p53 polypeptides, fragments or derivatives, consist of or comprise a sequence selected from the group consisting of FXCKNSC (SEQ ID NO:31) and FXCQNSC (SEQ ID NO:32), where X = any amino acid.

Page 24, lines 22-34

Transposon insertions lying adjacent to a p53 gene can be used to generate deletions of flanking genomic DNA, which if induced in the germline, are stably propagated in subsequent generations. The utility of this technique in generating deletions has been demonstrated and is well-known in the art. One version of the technique using collections of P element transposon induced recessive lethal mutations (P lethals) is particularly suitable for rapid identification of novel, essential genes in *Drosophila* (Cooley *et al.*, Science (1988) 239:1121-1128; Spralding *et al.*, PNAS (1995) 92:0824-10830). Since the sequence of the P elements are known, the genomic sequence flanking each transposon insert is determined either by plasmid rescue (Hamilton *et al.*, PNAS (1991) 88:2731-2735) or by inverse polymerase chain reaction (Rehm, website at ~~http://www.~~fruitfly.org/methods/). A more recent version of the transposon insertion

technique in male *Drosophila* using P elements is known as P-mediated male recombination (Preston and Engels, Genetics (1996) 144:1611-1638).

Page 26, lines 8-14

RNAi has also been successfully used in cultured *Drosophila* cells to inhibit expression of targeted proteins (Dixon lab, University of Michigan, website at ~~http://~~dixonlab.biochem.med.umich.edu/protocols/RNAiExperiments.html). Thus, cell lines in culture can be manipulated using RNAi both to perturb and study the function of p53 pathway components and to validate the efficacy of therapeutic or pesticidal strategies which involve the manipulation of this pathway. A suitable protocol is described in Example 13.

Page 28, lines 3-19

P elements, or marked P elements, are preferred for the isolation of loss-of-function mutations in *Drosophila* p53 genes because of the precise molecular mapping of these genes, depending on the availability and proximity of preexisting P element insertions for use as a localized transposon source (Hamilton and Zinn, Methods in Cell Biology (1994) 44:81-94; and Wolfner and Goldberg, Methods in Cell Biology (1994) 44:33-80). Typically, modified P elements are used which contain one or more elements that allow detection of animals containing the P element. Most often, marker genes are used that affect the eye color of *Drosophila*, such as derivatives of the *Drosophila white* or *rosy* genes (Rubin and Spradling, *supra*; and Klemenz *et al.*, Nucleic Acids Res. (1987) 15(10):3947-3959). However, in principle, any gene can be used as a marker that causes a reliable and easily scored phenotypic change in transgenic animals. Various other markers include bacterial plasmid sequences having selectable markers such as ampicillin resistance (Steller and Pirrotta, EMBO. J. (1985) 4:167-171); and *lacZ* sequences fused to a weak general promoter to detect the presence of enhancers with a developmental expression pattern of interest (Bellen *et al.*, Genes Dev. (1989) 3(9):1288-1300). Other examples of marked P elements useful for mutagenesis have been reported (Nucleic Acids Research (1998) 26:85-88~~; and http://flybase.bio.indiana.edu~~).

Page 44 line 31 through page 45 line 14

Analysis of sequences was done as follows: the traces generated by the automated sequencers were base-called using the program "Phred" (Gordon, Genome Res. (1998) 8:195-202), which also assigned quality values to each base. The resulting sequences were trimmed for quality in view of the assigned scores. Vector sequences were also removed. Each sequence was compared to all other fly EST sequences using the BLAST program and a filter to identify regions of near 100% identity. Sequences with potential overlap were then assembled into contigs using the programs "Phrap", "Phred" and "Consed" (Phil Green, University of Washington, Seattle, Washington; website at ~~http://~~bozeman.mbt.washington.edu/phrap.docs/phrap.html). The resulting assemblies were then compared to existing public databases and homology to known proteins was then used to direct translation of the consensus sequence. Where no BLAST homology was available, the statistically most likely translation based on codon and hexanucleotide preference was used. The Pfam (Bateman *et al.*, Nucleic Acids Res. (1999) 27:260-262) and Prosite (Hofmann *et al.*, Nucleic Acids Res. (1999) 27(1):215-219) collections of protein domains were used to identify motifs in the resulting translations. The contig sequences were archived in an Oracle-based relational database (FlyTag™, Exelixis Pharmaceuticals, Inc., South San Francisco, CA).

Page 47, line 27 through page 48, line 4

The DMp53 DNA and protein sequences were used to query sequences from *Tribolium, Leptinotarsa, and Heliothis* cDNA libraries using the BLAST computer program, and the results revealed several candidate cDNA clones that might encode p53 related sequences. For each candidate p53 cDNA clone, well-separated, single colonies were streaked on a plate and end-sequenced to verify the clones. Single colonies were picked and the plasmid DNA was purified using Qiagen REAL Preps (Qiagen, Inc., Valencia, CA). Samples were then digested with appropriate enzymes to excise insert from vector and determine size. For example, the vector pOT2, (website at ~~www.~~fruitfly.org/EST/pOT2vector.html) can be excised with Xho1/EcoRI; or

pBluescript (Stratagene) can be excised with BssH II. Clones were then sequenced using a combination of primer walking and *in vitro* transposon tagging strategies.

Page 48, lines 5 through 9

For primer walking, primers were designed to the known DNA sequences in the clones, using the Primer-3 software (Steve Rozen, Helen J. Skaletsky (1998) Primer3. Code available at ~~http://www-~~genome.wi.mit.edu/genome_software/other/primer3.html.). These primers were then used in sequencing reactions to extend the sequence until the full sequence of the insert was determined.

Page 59, lines 8 through 15

RNAi experiment in tissue culture: RNAi was performed essentially as described previously ~~(http://dixonlab.biochem.med.umich.edu/protocols/RNAiExperiments.html)~~. On day 1, cultures of Drosophila S2 cells were obtained that expressed pMT-HA-DMp53 expression plasmid and either 15 μg of DMp53 dsRNA or no RNA was added to the medium. On the second day, $CuSO_4$was added to final concentrations of either 0, 7, 70 or 700 μM to all cultures. On the fourth day, an alamarBlue (Alamar Biosciences Inc., Sacramento, CA) staining assay was performed to measure the number of live cells in each culture, by measuring fluorescence at 590 nm.